REMARKS

This document is filed in reply to the Office Action dated March 23, 2007 ("Office Action"). Applicant has amended the specification and claim 1 to promote clarity. Support for the amendment appears in, e.g., the abstract and Example 4 in the specification. No new matter has been introduced.

Upon entry of the proposed amendments, claims 1-21 will be pending. Among them, claims 2-4, 6-10, 12, 13, and 18-21 have been withdrawn for covering a non-elected invention. Claims 1, 5, 11, and 14-17 will be under examination. Reconsideration of this application is requested in view of the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 5, 11, and 14-16 for lack of enablement. Original claim 1 covered a method for increased therapeutic gain in chemotherapy or radiotherapy for proliferating malignant or nonmalignant disease to produce high probability of tumor control with low frequency of sequelae of [cancer] therapy. It is the Examiner's position that the claim is not enabled "because no mechanism of action or data is provided to support ... 'increased therapeutic gain [measured] with low frequency of sequelae of therapy." See the Office Action, pages 2-3, carryover paragraph.

Applicant has amended claim 1. This claim, as amended, is drawn to a method for increased therapeutic gain in chemotherapy or radiotherapy for proliferating malignant or nonmalignant disease. The method includes administrating a composition containing a histone hyperacetylating agent and a pharmaceutically acceptable carrier or a pharmaceutically acceptable salt thereof to a subject in need. The therapeutic gain includes preventing radiation or chemotherapy-induced complications or sequelae of mucositis, dermatitis, ulceration, tissue necrosis, fibrosis, xerostomia, plantar-palmar syndrome, and tumorigenesis, protecting normal tissues from cell death, and promoting radiation-induced wound healing in mucositis and dermatitis.

Applicant would like to point out that the specification provides ample guidance showing that administrating a composition containing a histone hyperacetylating agent to a subject leads to the therapeutic gain as mentioned above, and teaches how to administer the compostion. See, e.g., page 13, line 3 to page 16, line 16. Furthermore, the specification provides a number of working examples and data, demonstrating that administering of compositions containing histone hyperacetylating agents to a subject in fact brought about the therapeutic gain. More specifically, it was shown that a composition containing a histone hyperacetylating agent (such as phenylbutyrate) reduced acute radiation-induced normal tissue damage (see Example 3); suppressed radiation-induced skin damage including acute dermatitis and desquamation, and late fibrosis, ulceration and necrosis by promotion of wound healing (see Example 4); suppressed expression of inflammatory and fibrogenic cytokine (see Example 5) and expression of TGF-β or TGF-α in irradiated skin (see Examiners 6 and 7). The specification also provides working examples and data, showing that administration of compositions containing histone hyperacetylating agents (such as phenylbutyrate, trichostatin A and valproic acid) prevented late radiation-induced tumorigenesis or mucositis (see Examples 8-10). In view of these teachings, one skilled in the art would appreciate that administration of the compositions would result in therapeutic gain. He or she would also know how to practice the claimed method.

In view of the above amendments and remarks, Applicant submits that amended claim 1 meets the enablement requirement. Claims 5, 11, and 14-15 depend from claim 1 and further specify particular aspects of the claimed method. At least for the same reasons, they also meet the requirement.

Rejections under 35 U.S.C. § 103

Claims 1, 5, 11, and 14-16 were rejected as being obvious over U.S Patent No. 5,877,213 to Samid ("Samid"). See the Office Action, page 4, lines 14-15.

According to the Office Action, Samid describes methods of treating cancer with phenylacetic acid and its pharmaceutically acceptable sales and derivatives, such as sodium phenybutyrate, in combination with conventional radiotherapy. See page 4, line 16 to page 5, line 6. As such, the Examiner proceeds to conclude that "it would have been *prima facie* obvious to one of ordinary skill in the art to administer sodium phenybutyrate in the manner prescribed by Samid, in combination with radiotherapy, as a method of treating various cancer." See the Office Action, page 5, second paragraph.

Applicant has amended claim 1 and will discuss this claim 1 first. As mentioned above, this claim, as amended, is drawn to a method for increased therapeutic gain in chemotherapy or radiotherapy for proliferating malignant or nonmalignant disease. The therapeutic gain is limited to preventing radiation or chemotherapy-induced complications or sequelae of mucositis, dermatitis, ulceration, tissue necrosis, fibrosis, xerostomia, plantar-palmar syndrome, and tumorigenesis, protecting normal tissues from cell death, and promoting radiation-induced wound healing in mucositis and dermatitis. Here, the therapeutic gain as recited in the claim is directed to protecting normal tissues or repairing wounded tissue. In other words, the therapeutic gain and the method entail promoting cell proliferation and survival, and cell death is not desirable. In contrast, Samid focus on treating cancer, which entails killing and removing cells. Samid does not teach or suggest protecting normal tissue or preventing radiotherapy-induced complication or sequelae. Thus, there is no *prima facie* case of obviousness.

A *prima facie* case for obviousness requires more than the mere possibility of modifying a cited reference. As MPEP 2143.01 states: "[a] statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references" (emphasis added). Even there were a

prima facie case of obviousness, which Applicant does not agree, it can be successfully rebutted by a showing of an unexpected property of the claimed methods. As disclosed in the specification, the claimed method is capable of stimulating multiple cytokines or growth factors in the early phase of wound healing, and suppressing fibrogenic cytokines/growth factors in the late phase of tissue remodeling in the radiation-induced wound site. It is also useful in promoting epithelial cell re-growth and reducing excessive collagen accumulation, thus achieving rapid wound closure with reduced scaring. See page 1, lines 20-25, Examples 5 and 10; se also Figs. 4A-4D, and Fig. 9. All of these features were unexpected.

For the reasons and facts set forth above, Applicant submits that claim 1 is non-obvious over Samid. So are claims 5, 11, and 14-16, all of which depend from claim 1 directly or indirectly.

The Examiner further rejected claims 1 and 17 as being obvious over Samid in view of Shufeng *et al.*, Investigational New Drugs, vol. 20, 2002 ("Shufeng"). See the Office Action, page 5, lines 12-16. Samid has been discussed above. Shufeng describes a compound as an investigational anti-cancer drug, which may have a potential role in cancer treatment when co-administered with other drugs. See the Office Action, pages 5-6, carryover paragraph. Applicants would like to point out that Shufeng does not rectify the deficiency of Samid as described above. Thus, at least for the same reasons set forth above, claims 1 and 17 are non-obvious over Samid in view of Shufeng.

Conclusion

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any

claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Please apply any other charges or credits to Deposit Account No. 50-4189, referencing Attorney Docket No. 55701-004002.

Respectfully submitted,

Date: 6-22-2007

Jianming Hao, Ph.D.
Reg. No. 54,694

Customer No. 69713
Occhiuti Rohlicek & Tsao LLP
10 Fawcett Street
Cambridge, MA 02138
Telephone: (617) 500-2500
Facsimile: (617) 500-2499

877.doc